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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/599,002 | 06/22/2000 | Harold Inge Nyland | Q59836 | 8578 |

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| EXAMINER | |
|---|---|
| JOHANNSEN, DIANA B | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/599,002 | NYLAND ET AL. | |
| | Examiner | Art Unit | |
| | Diana B. Johannsen | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15,17-32 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,17,21,23-32 and 36* is/are rejected.

7)☒ Claim(s) *18-20 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***FINAL ACTION***

1. This action is in response to the Amendment filed May 7, 2003. Claims 15, 17, and 23-31 have been amended, claim 16 has been canceled, and claim 36 has been added. Claims 15, 17-32, and 36 are now pending and under consideration. The amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Objections***

**THE FOLLOWING ARE NEW GROUNDS OF OBJECTION NECESSITATED BY APPLICANTS' AMENDMENTS TO THE CLAIMS:**

3. Claims 18-20 and 22 are objected to as being dependent upon a rejected base claim. While the claims are no longer rejected (as a result of Applicants' amendments and arguments; see further discussion below), the claims are now in an improper form, by virtue of being unrejected claims that depend from a rejected base claim.

***Claim Rejections - 35 USC § 112***

4. In view of the cancellation of claim 16, the rejections of that claim under 35 U.S.C. 112, first paragraph and 35 U.S.C. 112, second paragraph are moot.

5. In view of the amendment of claim 15 such that claim 15 and claims dependent therefrom are limited to human subjects, the rejection of dependent claims 18-22 under 35 U.S.C. 112, first paragraph is withdrawn. It is noted that the enablement of the

embodiment of claim 22 was discussed further in the Interview Summary of November 19, 2002. It is also noted that applicants' arguments regarding the embodiment of claim 21 were found to be persuasive.

**6.** Claims 15, 17, 23-32, and 36 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth below and in the Office action of November 7, 2002. **It is noted that Applicants' amendments necessitated the inclusion of claim 36 in this rejection.**

The response traverses the rejection on the following grounds. The response notes that the claims have been amended to recite an "Fcγ receptor" rather than any "Fc" receptor. The response argues that applicants' invention "is based on the finding that variants of Fcγ receptors are associated with the specific diseases as set out in Claim 15, and that, once this has been ascertained, it is straightforward (i.e., would involve no undue experimentation) for the skilled person, based on the teachings of the specification, to compare the genotypes of Fcγ receptors from normal subjects and diseased subjects in accordance with the method of Claim 15 in order to determine whether a non-benign or benign prognosis should be given for the specified diseases." The response also states that "the steps in Claim 15, and also the specification on page 8, lines 4-22, describe that it is straightforward to determine the benign or non-benign genotypes for particular Fcγ receptors for the selected diseases."

Applicants' arguments have been thoroughly considered but are not persuasive. It is acknowledged that applicants' amendment to the claims (such that the claims are limited to a particular type of Fc receptors, Fcγ receptors) narrows the scope of the

claims, and further that the steps required to ascertain and compare sample genotypes are routine in the art. However, it is well-known to those of skill in the art (as discussed at, e.g., pages 5-6 of applicants' specification), that there are multiple classes of Fcγ receptors, which different receptors are encoded by a variety of genes that further produce a number of variants having different properties. Further, it is noted that the term "genotype" is a general term that encompasses any type of "genotype" that may be determined by one of skill in the art; this general term is not limited to the particular genotypes recited in applicants' specification. As discussed in the Office action of November 7, 2002, the teachings of the specification and of the art establish associations between certain particular genotypes of particular Fcγ receptor types and some specific conditions encompassed by the claims. However, the claims as written encompass the detection of any genotype of any of these receptor genes with any of the conditions recited in the claims, and thus, the teachings of the specification and of the art are enabling for only a small fraction of the numerous embodiments encompassed by the claims. While one of skill in the art could certainly perform further experimentation to establish whether additional relationships exist between, e.g., other particular Fcγ receptor genotypes and the conditions encompassed by the claims, the outcome of such experimentation cannot be predicted. Accordingly, it is unpredictable as to whether any quantity of experimentation would be sufficient to enable applicants' invention in a manner reasonably commensurate with the instant claims. Regarding claim 36, it is further noted that while the claim is limited to particular genotypes, the claim as written is not limited to a relationship between said genotypes and any

particular condition (as in, e.g., claims 18-22), but rather encompasses an association between the recited genotypes and either a benign or non-benign prognosis for any of the conditions recited in claim 15. It is unknown and unpredictable as to whether any relationship exists between the recited genotypes and the majority of the conditions recited in the claim, and it is unknown as to whether any quantity of experimentation would actually result in the determination that such a relationship even exists. Accordingly, it would require undue experimentation to use applicants' invention in a manner reasonably commensurate with the claims, and therefore this rejection is maintained.

***Claim Rejections - 35 USC § 102***

7. In view of the cancellation of claim 16, the rejection of that claim under 35 U.S.C. 102(b) as being clearly anticipated by Kimberly et al (WO 96/06952 [3/1996]) is moot.

**8.** Claims 15, 17, 23, 26-27, 30-32, and 36 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kimberly et al (WO 96/06952 [3/1996]), for the reasons set forth below and in the Office action of November 7, 2002. **It is noted that Applicants' amendments to the claims necessitated the inclusion of new claim 36 in this rejection.**

Kimberly et al disclose methods of diagnosing "predisposition to severe forms of autoimmune disease" comprising steps of determining patterns of Fcγ receptor alleles in a patient and comparing those patterns to control patterns characterizing populations free of disease and/or having disease of different levels of severity in order to determine the patient's prognosis (see entire reference, especially, e.g., page 4). The methods

disclosed by Kimberly et al include methods in which predisposition to "severe forms" of Wegener's granulomatosis is determined by identifying a patient's pattern of Fcγ RIIIB alleles (p. 4). It is an inherent property of Wegener's granulomatosis that it characterized by systemic vasculitis and constitutes a type of "cardiovascular disease." Kimberly et al provide evidence that Fcγ RIIIB genotype NA1/NA1 is more prevalent in Wegener's patients than in a normal population (see Example 6). Regarding claims 26-27, Kimberly et al disclose further steps of administering agents that constitute "prophylactic or therapeutic" materials to patients having a non-benign prognosis (see, e.g., p. 6). Regarding claim 32, it is noted that the methods employed by Kimberly et al employ allele-specific probes (see Example 6). Regarding new claim 36, it is again noted that Kimberly et al provide evidence that Fcγ RIIIB genotype NA1/NA1 is more prevalent in Wegener's patients than in a normal population (see Example 6).

The response traverses the rejection on the following grounds. The response argues that Wegener's granulomatosis (WG) is not a type of cardiovascular disease. The response cites a definition of WG from "Harrison's principles of internal medicine, 14th edition," and argues that while Harrison's teaches that WG may involve vasculitis of small arteries, "Small vessels do not include major cardiac or neck/brain vessels, i.e., cardiovascular disease is not part of this "small-vessel vasculitis."

Applicants' arguments have been thoroughly considered, but are not persuasive. It is first noted that the reference cited by applicant has not been provided to the examiner with Applicants' response or otherwise cited during prosecution of the instant application; accordingly, it is not clear whether the excerpt quoted by applicant is a

complete definition of WG or merely a portion thereof. However, while it is acknowledged that the features of WG described in applicants' arguments would be well-known to a skilled artisan as characteristics of WG, it is again noted that, as indicated in the Office action of November 7, 2002, it is an inherent property of WG that it is a type of cardiovascular disease. One of ordinary skill in the art would not consider the broad and general term "cardiovascular disease" to be limited to conditions that only afflict vessels of a particular size, as suggested by Applicant. As further evidence that one of skill in the art would consider WG to be a cardiovascular disease, the examiner has enclosed the National Library of Medicine description of WG, and it is noted that WG is in fact indexed as a "cardiovascular disease". Accordingly, it is clear that an ordinary artisan would consider WG to be a type of "cardiovascular disease." Further, it is noted that applicants' specification does not include any type of limiting definition that would exclude WG or any other type of vasculitis from this broad and general terminology. Accordingly, applicants' arguments are not persuasive.

Kimberly et al teach all the limitations recited in present claims 15, 17, 23, 26-27, 30-32, and 36, and therefore this rejection is maintained.

***Claim Rejections - 35 USC § 103***

9. Claims 25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimberly et al (WO 96/06952 [3/1996]) in view of Herridge et al (Journal of Thoracic and Cardiovascular Surgery 111(5):961-966 [5/1996]), for the reasons set forth below and in the Office action of November 7, 2002.

The response traverses the rejection on the grounds that the Kimberly et al reference does not teach or suggest the invention of independent claim 15, for the reasons discussed previously, and further on the grounds that the Herridge et al reference "does not provide the deficiencies" which exist in the Kimberly et al reference.

These arguments have been thoroughly considered but are not persuasive. First, with regard to the Kimberly et al reference, the response traverses the rejection for the same reasons discussed in paragraph 8, above. Accordingly, the response to those arguments applies equally herein. Second, it is noted that the Herridge et al reference was not cited to overcome "deficiencies" of the Kimberly et al reference asserted by Applicants, but rather for its teaching of surgical treatment for symptoms of Wegener's granulomatosis, as discussed in the Office action of November 7, 2002. Accordingly, Applicants' arguments are not persuasive.

The combined references of Kimberly et al and Herridge et al suggest all the limitations of present claims 25 and 29, and therefore this rejection is maintained.

10. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kimberly et al in view of Bux et al (Blood 89(3):1027-1034 [2/1997]), for the reasons set forth below and in the Office action of November 7, 2002.

The response traverses the rejection on the following grounds. The response states that "Although Bux et al may disclose that the NA2/NA2 genotype is associated with neutropenia in some individuals, Applicants respectfully submit that Bux et al can not be interpreted to indicate that a causal link or an increased risk is demonstrated between neutropenia and cerebral haemorrhage," and further states that "only one in

four of the cases reported in Bux et al (case report No. 2 in column 2 on page 1027) suffered a cerebral haemorrhage." The response argues that "this cerebral haemorrhage could have been caused by any number of factors other than neutropenia," and notes in particular that "the neonate who suffered the cerebral haemorrhage was quite premature and that any one of many complications arising from this premature birth, for example the severe respiratory distress which was suffered by this neonate, are likely to have caused or given rise to the increased risk of the cerebral haemorrhage." The response further argues that "the cerebral haemorrhage observed in case report No. 2 is no more than coincidence with the NA2/NA2 genotype," and that "there is no evidence from Bux et al that neutropenia positively triggers or results in an increased risk of cerbral haemorrhage, and hence there is no reason that a skilled person would have combined" the teachings of the references.

Applicants' arguments have been thoroughly considered but are not persuasive. It is first noted that the instant claim is not limited to an embodiment of Applicants' invention for which unexpected results have been shown (e.g., a method in which a particular genotype is detected as an indicator of a specific condition, and for which data is provided in the specification), but rather encompasses any method in which the NA2/NA2 genotype is indicative of a non-benign prognosis for any "cerebrovascular disease, cardiovascular disease, or atherosclerosis." It is acknowledged that of the 4 cases reported in Bux et al, only 1 of the 4 suffered a cerebral hemorrhage, and that it is apparent that cerebral hemorrhage does not occur in many patients suffering from neutropenia. However, the Bux et al reference does teach that neutropenia can cause

meningitis (see, e.g., page 1033), itself a disorder of which one well known complication is cerebral hemorrhage, and the Bux et al reference does establish that cerebral hemorrhage actually occurs in at least some neutropenia patients. Even if the chance that any particular neutropenia patient might develop a cerebral hemorrhage is small, one of ordinary skill in the art would have been motivated to have identified increased risk of neutropenia (and thereby to have identified increased risk for any of the possible complications of neutropenia, which complications include cerebral hemorrhage), as discussed in the Office action of November 7, 2002. Accordingly, Applicants' arguments are not persuasive.

The combined references of Kimberly et al and Bux et al suggest all the limitations of present claim 21, and therefore this rejection is maintained.

11. Claims 24 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimberly et al in view of Bux et al as applied to claim 21, above, and further in view of Van Nostrand et al (U.S. Patent No. 5,270,165 [12/1993]), for the reasons set forth below and in the Office action of November 7, 2002.

The response traverses the rejection on the grounds that "Claim 15 from which Claims 24 and 28 directly or indirectly depend, is not taught or suggested in Kimberly et al in view of Bux et al, and Van Nostrand et al does not provide the deficiencies which exists therein."

This argument has been thoroughly considered but is not persuasive. First, with respect to the Kimberly et al reference and/or Kimberly et al reference in combination with the Bux et al reference, the response traverse the rejection for the same reasons

set forth in paragraphs 8 and 10, above. Accordingly, the response to those arguments applies equally herein. Second, it is noted that the Van Nostrand et al reference was not cited to overcome "deficiencies" of the Kimberly et al and Bux et al references asserted by Applicants, but rather for its disclosure of cerebral hemorrhage diagnosis by imaging, as discussed in the Office action of November 7, 2002. Accordingly, Applicants' arguments are not persuasive.

The combined references of Kimberly et al, Bux et al and Van Nostrand et al suggest all the limitations of present claims 24 and 28, and therefore this rejection is maintained.

***Conclusion***

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
July 22, 2003

GARY BENZION, PH.D
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